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(71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK).

(72) Inventors: RASMUSSEN, Stella, Rudkjaer; 4 Borthigsgade, DK-2100 Copenhagen Ø (DK). GROENLUND, Per; 11 Bakkedraget, DK-3400 Hilleroed (DK).

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(54) Title: A WET GRANULATION METHOD FOR PREPARING A STABLE PHARMACEUTICAL FORMULATION

(57) Abstract

This invention relates to a novel granulate and a novel solid oral dosage formulation comprising an active ingredient and one or more carriers. Moreover the invention relates to a wet granulation method for preparing the granulate as well as wet granulation method for preparing the oral solid dosage form. The method comprises granulation of the mixture wherein the granulation is performed in a high shear mixer with a temperature regulating means for keeping the temperature below 40 °C.

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Title

A WET GRANULATION METHOD FOR PREPARING A STABLE PHARMACEUTICAL FORMULATION

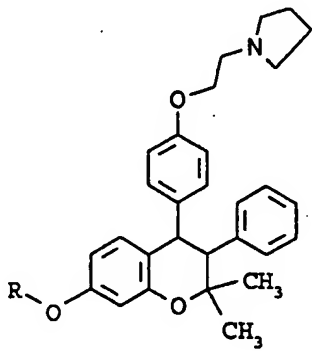
Field of the Invention

This invention relates to a novel granulate and a novel oral solid dosage formulation comprising an active ingredient and one or more carriers. Moreover the invention relates to a wet granulation method for preparing the granulate as well as a wet granulation method for preparing the oral solid dosage form.

Background of the Invention

High shear mixers are widely used in the pharmaceutical industry for blending and granulation (cf. Handbook of pharmaceutical granulation technology, chapter 7, "Drugs and the pharmaceutical sciences", vol. 81, 1997). Blending and wet massing is accomplished by high mechanical agitation by an impellar and chopper. High shear mixers have applications other than wet granulation, as it can be used for melt granulation and pelletization. When melt granulation or pelletization is performed, energy for melting the binder is supplied by agitation of the impellar and external heating of the bowl.

Compounds of formula I



(I)

wherein R is hydrogen or C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof, are described in i.a. U.S. Patent No. 5,280,040. This patent describes the preparation of

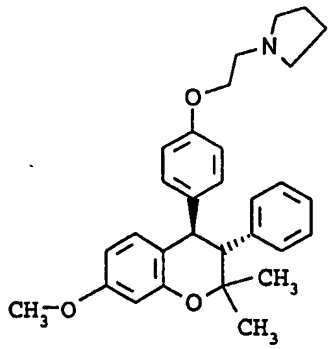
these compounds, as well as their use for reducing or preventing bone loss. The preparation of pharmaceutical compositions is also described.

Centchroman, which is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman, is a non-steroidal compound known to have antiestrogenic activity. It is in use in India as an oral contraceptive (see, for example, Salman et al., U.S. Patent No. 4,447,622; Singh et al., Acta Endocrinal (Copenh) 126 (1992), 444 - 450; Grubb, Curr Opin Obstet Gynecol 3 (1991), 491 - 495; Sankaran et al., Contraception 9 (1974), 279 - 289; Indian Patent Specification No. 129187). Centchroman has also been investigated as an anti-cancer agent for treatment of advanced breast cancer (Misra et al., Int J Cancer 43 (1989), 781 - 783. Recently, centchroman as a racemate has been found as a potent cholesterol lowering pharmaceutical agent expressed by a significant decrease of the serum concentrations (S.D. Bain et al., J Min Bon Res 9 (1994), S 394).

Levormeloxifene, (-) - 3R,4R - trans- 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane, is a particular preferred compound from this series of 3,4-diarylchromans. Levormeloxifene may be used in human and veterinary medicine for the regulation of bone metabolism. It may be used, for example, in the treatment of patients suffering from bone loss due to osteoporosis (including post-menopausal osteoporosis and glucocorticoid-related osteoporosis), Paget's disease, hyperparathyroidism, hypercalcemia of malignancy and other conditions characterized by excessive rates of bone resorption and/or decreased rates of bone formation.

The 3,4-diarylchromans are prepared according to known methods, such as those disclosed in U.S. Patent No. 3,340,276 to Carney et al., U.S. Patent No. 3,822,287 to Bolger, and Ray et al., J Med Chem 19 (1976), 276 - 279, the contents of which are incorporated herein by reference. Conversion of the cis isomer to the trans configuration by means of an organometallic base-catalyzed rearrangement is disclosed in U.S. Patent No. 3,822,287. The optically active d- and l-enantiomers may be prepared as disclosed by Salman et al. in U.S. Patent No. 4,447,622 (incorporated herein by reference) by forming an optically active acid salt which is subjected to alkaline hydrolysis to produce the desired enantiomer. The resolvation of (+/-) - 3,4-trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-

yl)ethoxy]phenyl}chromane in its optical antipodes is described in U.S. Patent No. 4,447,622 incorporated herein by reference. Example 1 of U.S. Patent No. 4,447,622 describes the preparation of the minus enantiomer, shown by formula II :



(II)

(In this specification, the compound of formula II is referred to as levormeloxifene.) In example 2 of U.S. Patent No. 4,447,622, levormeloxifene is obtained as the free base and the hydrochloride salt.

The compounds of formula I may be administered as pharmaceutically acceptable salts. A particularly useful pharmaceutically acceptable salt of levormeloxifene is the hydrogen fumarate salt. This salt form is prepared by dissolving fumaric acid and (-)-3R,4R- trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane in a common solvent such as e.g. methanol, and crystallizing the resulting salt from the solution.

Tiagabine is disclosed in US 5,010,090 incorporated herein by reference. (2E)-5-amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide is disclosed in WO 97/23508 incorporated herein by reference. Raloxifene is disclosed in US 4,418,068 and US 4,133,814 incorporated herein by reference. Idoxifene is disclosed in EP 260066 B1 and US 4,839,155 incorporated herein by reference. Tamoxifene is disclosed in US 4,536,516 incorporated herein by reference. 4-hydroxy Tamoxifene is disclosed in US 4,623,660 incorporated herein by reference. Toremifene is disclosed

in US 4,996,225 incorporated herein by reference. Droloxifene is disclosed in EP 792640 incorporated herein by reference.

An object of the present invention is to provide a novel granulate or oral solid dosage form with improved stability properties.

A further object of the present invention is to provide a novel tablet or capsule with possibility of extension of long term shelf-life.

Further objects of the present invention will become apparent from the specification.

Accordingly, the present invention relates to a wet granulation method for preparing a granulate comprising an active ingredient and one or more carriers, the method comprising

a) formation of a mixture of the active ingredient and one or more carriers,

b) granulation of the mixture and

c) drying the mixture,

wherein the granulation is performed in a high shear mixing means with a temperature regulating means for keeping the temperature below about 40°C in the mixture during granulation.

In another aspect of the present invention the wet granulation method for preparing a granulate comprising an active ingredient and one or more carriers, further comprises processing the granulate into an oral solid dosage formulation. In other words the present invention relates to a wet granulation method for preparing an oral solid dosage formulation comprising an active ingredient and one or more carriers, the method comprising

a) formation of a mixture of the active ingredient and one or more carriers,

b) granulation of the mixture,

c) drying the mixture, and

d) processing the granulate into an oral solid dosage formulation,

wherein the granulation is performed in a high shear mixing means with a temperature regulating means for keeping the temperature below about 40°C in the mixture during granulation. In one embodiment the oral solid dosage formulation is a tablet.. In another embodiment the oral solid dosage formulation is a capsule. In a

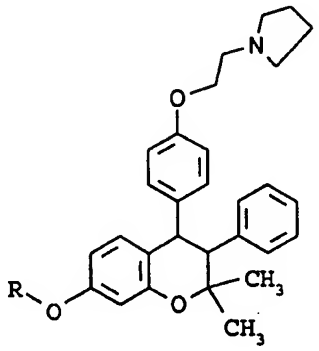
further embodiment the oral solid dosage formulation, such as tablet or capsule, is coated with a film.

In a further embodiment of the present method the temperature in the granulation mixture is lower than about 35°C. In a particular embodiment the temperature is from about 0°C to about 35°C, more preferred from about 0°C to about 30°C, even more preferred from about 0°C to about 25°C, still even more preferred from about 15°C to about 30°C, and most preferred from about 20°C to about 25°C. In still further embodiments of the present method, which embodiments should be considered independently of each other, the temperature in the granulation mixture is from about -20°C to about 40°C, from about -10°C to about 40°C, from about -10°C to about 0°C, from about 0°C to about 10°C, from about 10°C to about 20°C, from about 20°C to about 30°C, from about 30°C to about 40°C, from about 0°C to about 40°C, from about 10°C to about 35°C, from about 15°C to about 25°C, or from about 20°C to about 25°C.

In a further embodiment of the present method the active ingredient is selected from non-peptide organic molecules, small peptides and peptide mimetics. In one embodiment the active ingredient is a non-peptide organic molecule. In another embodiment the active ingredient is a small peptide. In a further embodiment the active ingredient is a peptide mimetic. In a further embodiment the active ingredient has a molecular weight of below 1500 daltons, such as from 200 to 1500 daltons, preferably from 500 to 1000 daltons.

In a further embodiment of the present method the active ingredient is selected from non-peptide organic molecules, small peptides and peptide mimetics, such as centchroman, levormeloxifene, tiagabine, (2E)-5-amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide, ipamorelin, raloxifene, idoxifene, tamoxifene and droloxifene or pharmaceutically acceptable salts thereof, each of which is considered to be an alternative embodiment. In a preferred embodiment the active ingredient is levormeloxifene or a pharmaceutically acceptable salt thereof, more preferred levormeloxifene hydrogen fumarate or levormeloxifene hydrogen maleate, most preferred levormeloxifene hydrogen fumarate.

In a still further embodiment of the present method the active ingredient is selected from a compound of formula I



(I)

wherein R is hydrogen or C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof. In one embodiment R is methyl. In another embodiment the compound of formula I is in the trans configuration. In a further embodiment the compound of formula I is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman (centchroman). In a still further embodiment the compound of formula I is an isolated l-enantiomer. In a further embodiment the compound of formula I is (-) - 3R,4R - trans-7-methoxy-2,2-dimethyl-3-phenyl-4-[4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane (levormeloxifene). In a still further embodiment the compound of formula I is in the form of the hydrogen fumarate salt. In a further embodiment the compound of formula I is in the form of the hydrogen maleate salt.

The one or more carriers are such which are commonly used in the pharmaceutical chemistry for preparing granulates, see eg. Remington: The Science and Practice of Pharmacy, 19th Edition (1995) and/or Handbook of pharmaceutical granulation technology, chapter 7, "Drugs and the pharmaceutical sciences", vol. 81, 1997. In a further embodiment of the present method the one or more carriers are selected from hydrophilic binders, water-soluble diluents, surfactants, detergents, lubricants, disintegrants, antioxidants, non water-soluble diluents and/or other fillers known to the skilled person. In a particular embodiment the one or more carriers comprises at least a hydrophilic binder and a water-soluble diluent.

In a further aspect the present invention relates to a granulate comprising an active ingredient and one or more carriers, obtainable by the wet granulation method

for preparing a granulate comprising an active ingredient and one or more carriers, the method comprising

a) formation of a mixture of the active ingredient and one or more carriers,

b) granulation of the mixture and

c) drying the mixture,

wherein the granulation is performed in a high shear mixing means with a temperature regulating means for keeping the temperature below about 40°C in the mixture during granulation. In one embodiment the granulate is obtained by said method.

In a still further aspect the present invention relates to an oral solid dosage formulation comprising an active ingredient and one or more carriers, obtainable by the wet granulation method for preparing an oral solid dosage formulation comprising an active ingredient and one or more carriers, the method comprising

a) formation of a mixture of the active ingredient and one or more carriers,

b) granulation of the mixture,

c) drying the mixture, and

d) processing the granulate into an oral solid dosage formulation,

wherein the granulation is performed in a high shear mixing means with a temperature regulating means for keeping the temperature below about 40°C in the mixture during granulation. In one embodiment the oral solid dosage formulation is obtained by said method. In another embodiment the oral solid dosage formulation is a tablet or capsule, preferably a tablet. In a particular embodiment of the oral solid dosage formulation the preferred range of total mass may be from about 40 mg to about 500 mg depending on the strength of the formulation, more preferred from about 80 mg to about 320 mg, most preferred from about 80 mg to about 120 mg.

In a special aspect of the above methods, if the wet massing step is left out in the disclosed wet granulation method a stable powder (instead of a stable granulation) will be obtained, which powder may be used for administration to a patient, eg. in solution or suspension, or may be compressed into an oral solid dosage form, eg. tablets.

Oral solid dosage formulations or compositions containing an active ingredient, eg. a compound of formula I may be administered one or more times per

day or week. An effective amount of such an active ingredient, eg. a compound of formula I is the amount required to effect prophylaxis or treatment of relevant disease-states. Such amount will depend, in part, on the particular disease-state and its severity, and age, weight, and general health of the patient, and other factors evident to those skilled in the art, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge. A typical daily dose will contain a nontoxic dosage range of from about 0.0001 to about 75 mg/kg patient per day of an active ingredient, eg. a compound of formula I, in particular levormeloxifene. A suitable dose of a compound of formula I, such as levormeloxifene, is e.g. from 0.01 to 2.5 mg per day to a patient, eg. a woman.

Definitions

As used herein, the term "C_{1-6}alkyl" includes straight and branched chain alkyl radicals containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like.

The term "a wet granulation method" represents a conventional way of making granules and is disclosed in eg. Remington: The Science and Practice of Pharmacy, 19th Edition (1995) and/or in Handbook of pharmaceutical granulation technology, chapter 7, "Drugs and the pharmaceutical sciences", vol. 81, 1997. The wet method usually comprises the steps of weighing, mixing, granulation, screening the damp mass, drying, and optionally dry screening, lubrication and compression.

The term "a granulate" is intended to mean the granulate obtainable by using the wet granulation method and has the general meaning as disclosed in eg. Remington: The Science and Practice of Pharmacy, 19th Edition (1995) and/or in Handbook of pharmaceutical granulation technology, chapter 7, "Drugs and the pharmaceutical sciences", vol. 81, 1997. The granules may have any suitable size, depending on the carriers and/or equipment used and the preparation of granules with a particular size and structure is within the technical knowledge of the skilled person.

The term "an active ingredient" is intended to mean any compound having a therapeutic effect, and which is suitable for administration as an oral solid dosage

formulation, such as non-peptide organic molecules, small peptides and peptide mimetics, and the like, as well as their pharmaceutically acceptable salts, in particular, but not limited to, a compound of formula I eg. centchroman or levormeloxifene; tiagabine, (2E)-5-amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide, ipamorelin, raloxifene, idoxifene, tamoxifene, 4-hydroxy tamoxifene, toremifene, or droloxifene or pharmaceutically acceptable salts thereof. The active ingredient itself may be stable upon storage or under stress conditions, but when formulated with one or more carriers it shows stability problems, eg. it starts to degrade.

The term "one or more carriers" is intended to mean such carriers which are commonly used in the pharmaceutical chemistry for preparing granulates and oral solid dosage formulations, see eg. Remington: The Science and Practice of Pharmacy, 19th Edition (1995) and/or Handbook of pharmaceutical granulation technology, chapter 7, "Drugs and the pharmaceutical sciences", vol. 81, 1997. In particular such one or more carriers are selected from, but not limited to, hydrophilic binders, water-soluble diluents, surfactants, lubricants, disintegrants, antioxidants, non water-soluble diluents and/or other fillers known to the skilled person.

The term "formation of a mixture of the active ingredient and one or more carriers" is intended to have its usual meaning, ie. mixing the active ingredient and carriers, in a suitable container, so as to form a mixture. For instance, the container may be the high shear mixing means wherein the granulation of the mixture takes place, but it is not limited hereto.

The term "granulation of the mixture" is intended to have its usual meaning, as disclosed in eg. Remington: The Science and Practice of Pharmacy, 19th Edition (1995) or in Handbook of pharmaceutical granulation technology, chapter 7, "Drugs and the pharmaceutical sciences", vol. 81, 1997; and include one or more of dry blending, wet massing, and after granulation.

The term "drying the mixture" is intended to have its usual meaning, as disclosed in eg. Remington: The Science and Practice of Pharmacy, 19th Edition (1995) or in Handbook of pharmaceutical granulation technology, chapter 7, "Drugs and the pharmaceutical sciences", vol. 81, 1997; and comprises drying the

granulation mixture in a conventional manner either inside or outside the high shear mixing means, such as, but is not limited to, by placing the moist granulation mixture in drying cabinets with circulating air current and thermostatic heat control.

The term "a high shear mixing means" is intended to mean a high shear mixer, high speed mixer or high shear granulator or similar mixer/granulator as disclosed in eg. Remington: The Science and Practice of Pharmacy, 19th Edition (1995) or in Handbook of pharmaceutical granulation technology, chapter 7, "Drugs and the pharmaceutical sciences", vol. 81, 1997; and comprises, but is not limited to, a high shear mixer, such as a high speed, high shear mixer, such as a vertical axis high shear mixer or a horisontal axis high shear mixer. The high shear mixer may be selected from the following types: Gral, Lodige/Littleford, Diosna, Fielder or Baker-Perkins.

The term "a temperature regulating means" is intended to comprise any such means that can increase or lower the temperature in a mixture, eg. contained in a high shear mixing means. Such temperature regulating means comprises, but is not limited to, internal or external temperature regulating means, such as an internal or external cooling mantle with a fluid such as cold water (4-5 °C), or internal cooling tubes, or dry ice added in the high shear mixing means, or the high shear mixing means may be placed in a larger container which operates as a freezer.

The term "a high shear mixing means with a temperature regulating means" is intended to mean that the high shear mixing means is either equiped with the temperature regulating means, which may constitute an integrated part thereof, or the temperature regulating means may be separate from the high shear mixing means and still regulate temperature, for instance if the high shear mixing means is placed in a larger container which operates as a freezer.

The term "during granulation" is intended to mean during the entire granulation period, or during a part or parts of the granulation period, such as, but not limited to, during wet massing.

The term "processing the granulate" is intended to mean the further conventional processing of the granulate into an oral solid dosage formulation as disclosed in eg. Remington: The Science and Practice of Pharmacy, 19th Edition (1995) or in Handbook of pharmaceutical granulation technology, chapter 7, "Drugs

and the pharmaceutical sciences", vol. 81, 1997; and comprises, but is not limited to, reducing the granulate to a particular size, lubrication, and compressing into tablets or filling into gelatine capsules.

The term "an oral solid dosage formulation" or "an oral solid dosage form" is intended mean such solid dosage formulations as disclosed in eg. Remington: The Science and Practice of Pharmacy, 19th Edition (1995) or in Handbook of pharmaceutical granulation technology, chapter 7, "Drugs and the pharmaceutical sciences", vol. 81, 1997; and comprises, but is not limited to, tablets, incl. chewable tablets, capsules, pills, lozenges, troches, cachets and pellets.

The term "pharmaceutically acceptable salt" represents salt forms of an active ingredient, eg. a compound of formula I, that are physiologically suitable for pharmaceutical use. The pharmaceutically acceptable salts can exist in conjunction with a compound of formula I as acid addition primary, secondary, tertiary, or quaternary ammonium, alkali metal, or alkaline earth metal salts. Generally, the acid addition salts are prepared by the reaction of an acid with an active ingredient, eg. a compound of formula I. The alkali metal and alkaline earth metal salts are generally prepared by the reaction of the metal hydroxide of the desired metal salt with a compound of formula I, wherein R is hydrogen.

Within the present invention, the active ingredient, eg. compounds of formula I may be prepared in the form of a salt such as pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, maleic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The term "hydrophilic binder" represents binders commonly used in the formulation of pharmaceuticals, such as polyvinylpyrrolidone, copolyvidone (cross-

linked polyvinylpyrrolidone), polyethylene glycol, sucrose, dextrose, corn syrup, polysaccharides (including acacia, tragacanth, guar, and alginates), gelatin, and cellulose derivatives (including hydroxypropyl methylcellulose, hydroxypropyl cellulose, and sodium carboxymethylcellulose).

The term "water-soluble diluent" represents compounds typically used in the formulation of pharmaceuticals, such as sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), and cyclodextrins.

The term "non water-soluble diluent" represents compounds typically used in the formulation of pharmaceuticals, such as calcium phosphate, calcium sulfate, starches, modified starches and microcrystalline cellulose.

The term "non water-soluble diluent with non-swelling properties" represents the non water-soluble diluents as indicated above, but excluding starches and modified starches and the like.

The term "surfactant", as used herein, represents ionic and nonionic surfactants or wetting agents commonly used in the formulation of pharmaceuticals, such as ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, sodium docusate, sodium laurylsulfate, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids.

The term "antioxidant" represents the three groups of antioxidants, true antioxidants, reducing agents and antoxidant synergists, such as tocopherols, tocopherolesters, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, ascorbic acid, citric acid, edetic acid and its salts, lecithin and tartaric acid.

The term "disintegrant" represents compounds such as starches, clays, celluloses, alginates, gums, cross-linked polymers (such as cross-linked polyvinylpyrrolidone and cross-linked sodium carboxymethylcellulose), sodium starch glycolate, low-substituted hydroxypropyl cellulose, and soy polysaccharides. Preferably, the disintegrant is a modified cellulose gum such as e.g. cross-linked sodium carboxymethylcellulose.

The term "lubricant" represents compounds frequently used as lubricants or glidants in the preparation of pharmaceuticals, such as talc, magnesium stearate, calcium stearate, stearic acid, colloidal silicon dioxide, magnesium carbonate, magnesium oxide, calcium silicate, microcrystalline cellulose, starches, mineral oil, waxes, glyceryl behenate, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, sodium laurylsulfate, sodium stearyl fumarate, and hydrogenated vegetable oils. Preferably, the lubricant is magnesium stearate or talc, more preferably magnesium stearate and talc in combination.

In one preferred embodiment of the invention, the hydrophilic binder is gelatin, cellulose derivative, polyvinylpyrrolidone or copolyvidone.

In another preferred embodiment of the invention, the water-soluble diluent is a sugar, a polysaccharide or cyclodextrin.

In another preferred embodiment of the invention, the formulation (granulate or oral solid dosage formulation) further comprises a non water-soluble diluent. In one embodiment thereof the non water-soluble diluent is a non water-soluble diluent with non-swelling properties, preferably microcrystalline cellulose.

In another preferred embodiment of the invention, the formulation further comprises an antioxidant. Preferably the antioxidant is tocopherols and tocopherolesters, such as alpha-tocopherol succinate.

In another preferred embodiment of the invention, the formulation further comprises a surfactant. When the surfactant is present, preferably it is an anionic or nonionic surfactant. Representative surfactants from this preferred group include sodium laurylsulfate, polyglycolyzed glycerides, polyoxyethylene sorbitan fatty acid esters, monoglycerides, diglycerides or glycerol.

In another preferred embodiment of the invention, the formulation further comprises a lubricant(s) and/or a disintegrant.

Certain formulations of the present invention are more preferred. More preferably, the hydrophilic binder is polyvinylpyrrolidone or copolyvidone. More preferably, the water-soluble diluent is a sugar, such as lactose, sucrose, dextrose. More preferably, the surfactant, when present, is a nonionic surfactant, such as polyoxyethylene sorbitan fatty acid esters or glycerol.

Certain formulations of the present invention are most preferred. Most preferably, the hydrophilic binder is copolyvidone. Most preferably, the water-soluble diluent is lactose.

The amount of hydrophilic binder in the pharmaceutical formulation according to the invention is preferably from about 1% to about 25% (w/w), more preferably from about 1% to about 15% (w/w), most preferably from about 2,5% to about 15% (w/w).

The amount of water-soluble diluent in the pharmacutical formulation according to the invention is preferably from about 20% to about 98% (w/w), more preferred from about 20% to about 80% (w/w).

The amount of non water-soluble diluent in the pharmacutical formulation according to the invention is preferably from about 1% to about 50% (w/w), more preferred from about 5% to about 30% (w/w).

The amount of the active ingredient, eg. compound of formula I, in the pharmaceutical formulation according to the invention is preferably from about 0,05% to about 50% (w/w), such as from about 0,1% to about 40% (w/w).

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Tablets for this invention are prepared utilizing conventional tabletting techniques. A general method of manufacture involves blending of a compound of formula I, or a salt thereof, the water-soluble diluent, hydrophilic binder and optionally a portion of a disintegrant. This blend is then granulated with an aqueous solution of the hydrophilic binder or an aqueous solution of the hydrophilic binder and surfactant and milled, if necessary. The granules are dried and reduced to a suitable size. Any other ingredients, such as lubricants, (e.g. magnesium stearate) and additional disintegrants, are added to the granules and mixed. This mixture is then compressed into a suitable size and shape using conventional tabletting machines such as a rotary tablet press. The tablets may be film coated by techniques well known in the art.

Capsules for this invention are prepared utilizing conventional methods. A general method of manufacture involves blending of a compound of formula I, or a salt thereof, the water-soluble diluent, a hydrophilic binder, and optionally a portion of

a disintegrant. This blend is then granulated with an aqueous solution of the hydrophilic binder or an aqueous solution of the hydrophilic binder and surfactant in water, and milled, if necessary.

The granules are dried and reduced to a suitable size. Any other ingredients, such as a lubricant, are added to the granules and mixed. The resulting mixture is then filled into a suitable size hard-shell gelatin capsule using conventional capsule-filling machines.

The preferred range of pharmaceutical formulation (such as oral solid dosage form, e.g. capsule or tablet) strength may be from about 0.1 mg to about 40 mg of a compound of formula I, more preferred from about 0.25 mg to about 5 mg of a compound of formula I, preferably levormeloxifene.

The preferred range of total mass may be from about 40 mg to about 500 mg depending on the strength of the formulation, more preferred from about 80 mg to about 320 mg.

Tablets and capsules may be prepared using the ingredients and procedures as described below.

The following examples and embodiments are illustrative only and are not intended to limit the scope of the invention in any way.

Experimental part

During the manufacturing of batches for clinical trail a granulation temperature of > 60°C was obtained. During the stability of these batches an increase in degradation products were observed and the high granulation temperature was suspected.

An investigation of the effect of the granulation temperature was initiated with the following temperature interval: < 0°C, < 10°C, 20 - 25°C, 40 - 45°C, > 70°C. The experiment was carried out in laboratory scale in a high shear mixer of 1 l carried out on tablet formulation with the following composition. (see formulation 1) After manufacture the tablets were stored in open container at stress conditions, 60°C.

The preliminary investigation showed that the granulation temperature had an effect on degradation products. At temperature lower than 20°C no further improvement in the stability of the levormeloxifene product was seen.

Based on the observation results further investigation was initiated and the results are described in tables 1 and 2.

Table 1: Investigation of granulation temperature.
Levormeloxifene 0.25 mg, total mass: 80 mg
Tablets stored at 60°C in open petri dishes

Granulation Temperature	Months of Storage	Degradation Products SUM (%)
20 - 25°C	0	0.68
	1	2.03
	2	3.27
	3	5.12
40 - 45°C	0	0.71
	1	2.63
	2	3.65
	3	6.07
> 70°C	0	0.76
	1	3.29
	2	4.89
	3	7.98

Table 2: Investigation of granulation temperature.
Levormeloxifene 0.25 mg, total mass: 120 mg
Tablets stored at 60°C in open petri dishes

Granulation Temperature	Months of Storage	Degradation Products SUM (%)
20 - 25°C	0	0.68
	1	2.68
	2	4.42
	3	6.30
40 - 45°C	0	0.78
	1	3.16
	2	4.74
	3	7.75
> 70°C	0	0.81
	1	4.15
	2	6.03
	3	10.41

The stability of a levormeloxifene formulation, such as the formulations disclosed in WO 98/23270, can be improved by lowering the process temperature in the high shear mixer, especially the granulation temperature below 40°C. The most optimal temperature interval is 20 - 25°C.

From the experiments in table 1 and table 2 it may be observed that the stability of a levormeloxifene formulation can be improved by lowering the total mass.

Formulation 1

Ingredient	Weight (mg/tablet)
Levormeloxifene fumarate corresponding to 1.25 mg base	1.57
Microcrystalline Cellulose	48.0
Cross-carmellose Sodium	25.0
Copolyvidone	24.0
Lactose	217
Magnesium Stearate	1.60
Talc	3.20

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. During granulation cooling is added. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 320 mg. It is possible to manufacture levormeloxifene tablet strenghts in the range of 1.25 mg to 40 mg with a total mass in the range of 160 mg to 320 mg.

Formulation 2

Ingredient	Weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.314
Microcrystalline Cellulose	15.5
Cross-carmellose Sodium	6.00
Copolyvidone	7.50
Lactose	69.2
Magnesium Stearate	0.500
Talc	1.00

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. During granulation cooling is added. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight with in the range of 80 mg to 160 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.1 mg to 5 mg with a total mass in the range of 80 mg to 160 mg.

In all of the below formulations 3-22 cooling is applied (added) during granulation.

Formulation 3

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	48.00 mg
Cross-carmellose sodium	25.00 mg
Copolyvidone	24.00 mg
Na-laurylsulfate	6.40 mg
Lactose	161.80 mg
Magnesium stearate	1.60 mg
Talc	3.20 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing dissolved sodium laurylsulfate. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 320 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40mg with a total mass in the range of 160 mg to 320 mg.

Formulation 4

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.314 mg
Microcrystalline cellulose	15.5 mg
Cross-carmellose sodium	6.00 mg
Copolyvidone	7.50 mg
Na-laurylsulfate	2.00 mg
Lactose	67.2 mg
Magnesium stearate	0.50 mg
Talc	1.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing dissolved sodium laurylsulfate. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight with in the range of 80 mg to 160 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.1 mg to 5 mg with a total mass with in the range of 80 mg to 160 mg.

Formulation 5

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Dextrose	168.20 mg
Microcrystalline cellulose	48.00 mg
Cross-carmellose sodium	25.00 mg
Copolyvidone	24.00 mg
Magnesium stearate	1.60 mg
Talc	3.20 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 320 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass in the range of 160 mg to 320 mg.

Formulation 6

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.314 mg
Dextrose	69.2 mg
Microcrystalline cellulose	15.5 mg
Cross-carmellose sodium	6.00 mg
Copolyvidone	7.50 mg
Magnesium stearate	0.50 mg
Talc	1.00 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight with in the range of 80 mg to 160 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.1 mg to 5 mg with a total mass with in the range of 80 mg to 160 mg.

Formulation 7

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	70.00 mg
Cross-carmellose sodium	31.25 mg
Gelatine	5.00 mg
Lactose	237.75 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass in the range of 160 mg to 400 mg.

Formulation 8

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.314 mg
Microcrystalline cellulose	15.5 mg
Cross-carmellose sodium	6.00 mg
Gelatine	1.50 mg
Lactose	75.2 mg
Magnesium stearate	0.50 mg
Talc	1.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight with in the range of 80 mg to 160 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.1 mg to 5 mg with a total mass with in the range of 80 mg to 160 mg.

Formulation 9

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	70.00 mg
Cross-carmellose sodium	31.25 mg
Dextrose	237.75 mg
Gelatine	5.00 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass in the range of 160 mg to 400 mg.

Formulation 10

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.314 mg
Microcrystalline cellulose	15.5 mg
Cross-carmellose sodium	6.00 mg
Dextrose	75.2 mg
Gelatine	1.50 mg
Magnesium stearate	0.50 mg
Talc	1.00 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight with in the range of 80 mg to 160 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.1 mg to 5 mg with a total mass with in the range of 80 mg to 160 mg.

Formulation 11

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	60.00 mg
Cross-carmellose sodium	31.25 mg
Copolyvidone	25.00 mg
Tween 80	3.25 mg
Lactose	224.50 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing Tween 80. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass in the range of 160 mg to 400 mg.

Formulation 12

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.314 mg
Microcrystalline cellulose	15.5 mg
Cross-carmellose sodium	6.00 mg
Copolyvidone	7.50 mg
Tween 80	0.80 mg
Lactose	68.4 mg
Magnesium stearate	0.50 mg
Talc	1.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing Tween 80. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight with in the range of 80 mg to 160 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.1 mg to 5 mg with a total mass with in the range of 80 mg to 160 mg.

Formulation 13

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	60.00 mg
Cross-carmellose sodium	31.25 mg
Copolyvidone	29.00 mg
Glycerol	3.25 mg
Lactose	220.50 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing glycerol. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass in the range of 160 mg to 400 mg.

Formulation 14

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.314 mg
Microcrystalline cellulose	15.5 mg
Cross-carmellose sodium	6.00 mg
Copolyvidone	7.50 mg
Glycerol	0.80 mg
Lactose	68.4 mg
Magnesium stearate	0.50 mg
Talc	1.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone containing glycerol. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight with in the range of 80 mg to 160 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.1 mg to 5 mg with a total mass with in the range of 80 mg to 160 mg.

Formulation 15

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	68.00 mg
Cross-carmellose sodium	26.25 mg
Gelatine	5.00 mg
Glycerol	6.25 mg
Dextrose	338.50 mg
Magnesium stearate	2.00 mg
Talc	4.00 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine and glycerol. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 400 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 40 mg with a total mass in the range of 160 mg to 400 mg.

Formulation 16

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.314 mg
Microcrystalline cellulose	15.5 mg
Cross-carmellose sodium	6.00 mg
Gelatine	1.50 mg
Glycerol	1.50 mg
Dextrose	74.5 mg
Magnesium stearate	0.50 mg
Talc	1.00 mg

The mixture of levormeloxifene fumarate, dextrose, microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine and glycerol. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight with in the range of 80 mg to 160 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.1 mg to 5 mg with a total mass with in the range of 80 mg to 160 mg.

Formulation 17

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 40 mg base	50.00 mg
Microcrystalline cellulose	35.00 mg
Cross-carmellose sodium	26.25 mg
hydroxypropyl-betacyclodextrin (HP-cd)	115.00 mg
Gelatine	5.00 mg
Glycerol	6.25 mg
Dextrose	256.50 mg
Magnseium stearate	2.00 mg
Talc	4.00

The mixture of levormeloxifene fumarate, dextrose, hydroxypropyl-betacyclodextrin microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine containing glycerol. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 500 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 1.25 mg to 80 mg with a total mass in the range of 160 mg to 500 mg.

Formulation 18

Ingredient	weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.314 mg
Microcrystalline cellulose	15.5 mg
Cross-carmellose sodium	6.00 mg
hydroxypropyl-betacyclodextrin (HP-cd)	28.8 mg
Gelatine	1.50 mg
Glycerol	1.50 mg
Dextrose	45.2 mg
Magnseium stearate	0.50 mg
Talc	1.00

The mixture of levormeloxifene fumarate, dextrose, hydroxypropyl-betacyclodextrin microcrystalline cellulose, and a portion of cross-carmellose sodium is granulated with an aqueous solution of gelatine containing glycerol. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight with in the range of 80 mg to 160 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.1 mg to 5 mg with a total mass with in the range of 80 mg to 160 mg.

Formulation 19 and 20

Ingredient	Weight
Levormeloxifene fumarate corresponding to 5 mg base	6.27 mg
Lactose	395.1 mg
Microcrystalline cellulose	9.875 mg
Polyvinylpyrrolidone/copolyvidone	8.400 mg
Magnesium stearate	0.375 mg

The mixture of levormeloxifene fumarate, lactose and microcrystalline cellulose is granulated with an aqueous solution of polyvinylpyrrolidone or copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate. The mixture is then filled into size 0 hard-shell gelatine capsules utilizing conventional encapsulating equipment. In order to obtain different capsule strenghts in the range of 0.18 mg to 7.50 mg, different quantities are weighed out in the range of 15 mg to 500 mg.

Formulation 21

Ingredient	Weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.313 mg
Microcrystalline Cellulose	12.00 mg
Cross-Carmellose Sodium	6.25 mg
Copolyvidone	6.00 mg
Lactose	54.20 mg
Alpha-tocopherol Succinate	0.0308 mg
Magnesium Stearate	0.40 mg
Talc	0.80 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, antioxidant, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 80 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.125 mg to 10 mg with a total mass in the range of 80 mg to 160 mg.

Formulation 22

Ingredient	Weight (mg/tablet)
Levormeloxifene fumarate corresponding to 0.25 mg base	0.314 mg
Microcrystalline Cellulose	15.00 mg
Cross-Carmellose Sodium	7.75 mg
Copolyvidone	7.50 mg
Lactose	64.80 mg
Alpha-tocopherol Succinate	0.0308 mg
Magnesium Stearate	0.50 mg
Talc	1.00 mg

The mixture of levormeloxifene fumarate, lactose, microcrystalline cellulose, antioxidant, and a portion of cross-carmellose sodium and copolyvidone is granulated with an aqueous solution of copolyvidone. The granules are dried, reduced to a suitable size and mixed with magnesium stearate, talc and remaining cross-carmellose sodium. The mixture is compressed into individual tablets yielding a tablet weight of 100 mg. It is possible to manufacture levormeloxifene tablet strengths in the range of 0.125 mg to 20 mg with a total mass of 100 mg.

Claims

1. A wet granulation method for preparing a granulate comprising an active ingredient and one or more carriers, the method comprising granulation of the mixture wherein the granulation is performed in a high shear mixing means with a temperature regulating means for keeping the temperature below about 40 °C in the mixture during granulation.

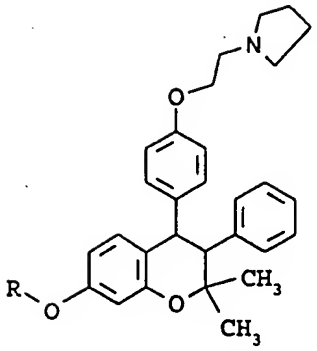
2. The method according to claim 1 further comprising processing the granulate into an oral solid dosage formulation.

3. A wet granulation method for preparing an oral solid dosage formulation comprising an active ingredient and one or more carriers, the method comprising granulation of the mixture and processing the granulate into an oral solid dosage formulation, wherein the granulation is performed in a high shear mixing means with a temperature regulating means for keeping the temperature below about 40 °C in the mixture during granulation.

4. The method according to any one of the claims 1-3 wherein the temperature in the granulation mixture is from about -10 °C to 35 °C.

5. The method according to any one of the claims 1-4 wherein the active ingredient is selected from non-peptide organic molecules, small peptides and peptide mimetics, such as centchroman, levormeloxifene, tiagabine, (2E)-5-amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide, raloxifene, idoxifene, toremifene, tamoxifene, 4-hydroxy tamoxifene and droloxifene or pharmaceutically acceptable salts thereof.

6. A wet granulation method for preparing a granulate comprising a compound of formula I



(I)

wherein R is hydrogen or C_{1-6}alkyl; or a pharmaceutically acceptable salt thereof and one or more carriers, the method comprising

a) formation of a mixture of the compound of formula I and one or more carriers,

b) granulation of the mixture and

c) drying the mixture,

wherein the granulation is performed in a high shear mixing means with a temperature regulating means for keeping the temperature below about 40 °C in the mixture during granulation.

7. The method according to claim 6 further comprising processing the granulate into an oral solid dosage formulation.

8. The method according to any one of the claims 6 or 7 wherein the temperature in the granulation mixture is from about -10 °C to 35 °C.

9. The method according to any one of the claims 6-8 wherein said compound of formula I is (-) - 3R,4R - trans- 7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}chromane.

10. The method according to any one of the claims 1-9 wherein said one or more carriers comprises a hydrophilic binder and a water-soluble diluent.

11. A granulate comprising an active ingredient and one or more carriers, obtainable by the method according to any one of the claims 1-10.

12. An oral solid dosage formulation comprising an active ingredient and one or more carriers, obtainable by the method according to any one of the claims 2-5 or 7-10.

13. The oral solid dosage formulation according to claim 12 wherein the formulation is a tablet or capsule.

14. The oral solid dosage formulation according to claim 13 wherein the formulation is a tablet.

15. The oral solid dosage formulation according to claims 13 or 14 wherein the formulation further comprises a film coating.

16. The oral solid dosage formulation according to claims 12-15 wherein the range of total mass of said formulation is from about 40 mg to about 500 mg.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00416

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/16, A61K 9/20
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	The 25th international symposium on controlled release of bioactive materials and the first consumer and diversified products conference, Publisher: Conatrolled Release Society, Inc. vol. 25, 1998, L. Liu et al: "The effect of process variables on a wet-granulation by high-shear mixer and fluid bed granulator of a novel hydrophilic matrix system", jun 1998, page 970 - page 971, see page 971 left column ---	1-16
A	International Journal of Pharmaceutics, Volume 156, 1997, Johan A. Westerhuis et al, "Multivariate modelling of the tablet manufacturing process with wet granulation for tablet optimization and in-process control", page 110 - page 117, see page 116 right column, lines 11 14 ---	11-14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1999	07 -12- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Yvonne Siösteen/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00416

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Pharm. Ind., Volume 52, No 9, 1990, T. Schaefer et al, "Wet Granulation i a Laboratory Scale High Shear Mixer", page 1147 - page 1153, see page 1150, fig. 4	1-16
A	International Journal of Pharmaceutics, Volume 92, 1993, G.J.B. Horsthuis et al, "Studies on upscaling parameters of the Gral high shear granulation process", page 143 - page 150, see page 146, fig. 3	1-16
A	Drug development and industrial pharmacy, Volume 19, No 13, 1993, P. Wehrlé et al, "Response surface methodology: an interesting statistical tool for process optimization and validation: example of wet granulation i a high-shear mixer" page 1637 - page 1653	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT DK/1999/00416

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims is found to be partly unsearchable because the scope of the claim is so broad. The feature "preparing a granulate comprising an active ingredient" of claim one is too general and does not disclose the invention in a sufficiently concise manner.

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.